This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

AMVAC

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Date: 19-Jan-99

SUBJECT: ADDITIONAL INFORMATION ON THE DOSING OF GUINEA PIGS WITH DDVP

Dear Dennis,

At the SAP meeting on 30 July 1998 many unanswered questions were raised regarding the discussion pertaining to the paper by Mehl et al, entitled "The effect of trichlorfon and other organophosphates on prenatal brain development, in the guinea pig" (Neurochemical Research, Vol 19, No. 5, 1994, pp569-574).

In light of these unanswered questions it was thought important to obtain clarification directly from the authors in order to aid in the interpretation of the study. One of Amvac's scientists, Ann Manley, visited with the authors of the paper in Norway. Her report is attached. It is important to note that there is no more available documentation on this guinea pig work and that most of the additional details that were clarified at the recent laboratory visit were mainly recollections from memory of all four study authors. Bearing in mind that these experiments with DDVP were carried out as long as 10 years ago, Amvac is confident that this is as accurate a reflection as possible of their work.

We learned several startling facts regarding the study conduct and the findings that directly impact the interpretation of the study.

1. The route of exposure to DDVP was subcutaneous. This was not mentioned in the publication.
2. The single animal that was dosed with 15 mg/kg of DDVP SC. had clinical signs of cholinesterase toxicity including involuntary jaw movements and salivation. This mother, although clearly indicating signs of OP toxicity, had offspring that had normal brain development. The authors considered this dose a no effect level.
3. An animal dosed with 20 mg/kg of DDVP subcutaneously had signs of severe organophosphate toxicity. This animal was not studied further. More importantly, this information was not included in the publication. The authors did not offer a reason for deleting this critical information. This data establishes a dose of 20 mg/kg as a near lethal dose. Therefore, the 15 mg/kg is certainly documented to be as high a dose as can be tested but no fetal effects were observed.
4. The 2 animals dosed with 30 mg/kg of DDVP had clear signs of cholinesterase poisoning. Data from these animals were pooled in the paper for analysis, however, the dose regime was different for each of these animals during the study.

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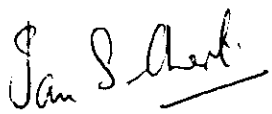
5. The animals treated with DDVP were dosed on separate occasions over a period of several years but the data reported as if it was one experiment.
6. The study had no Quality Assurance, was not performed to GLP standards and laboratory records could not be located.

In light of this information, it is totally inappropriate to use this data as a basis for a regulatory decision. It is arbitrary for the Agency to request us to repeat a study when the limited findings are at near lethal range from an exposure route wholly inappropriate for a pesticide. In particular, the allocation of an additional x3 ('FQPA') factor is not defensible where no selective fetal toxicity is demonstrated.

After reviewing these data Amvac would welcome the opportunity to discuss this study, and its ramifications, with the Agency as soon as possible.

Regards



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Bill Feiler
Jon Wood

PUBLISHED PAPER: *Neurochemical Research, Vol 19, No. 5, 1994, pp569-574.*

'THE EFFECT OF TRICHLORFON AND OTHER ORGANOPHOSPHATES ON PRENATAL BRAIN DEVELOPMENT, IN THE GUINEA PIG.'

Anna Mehl[1,2], Tore M. Schanke[1], Bjorn A. Johnsen[2] and Frode Fonnum[2].
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This publication which is in the open literature, is part of an unwritten graduate thesis of Anna Mehl. Dichlorvos (DDVP) was one of several organophosphates that were tested in the pregnant guinea pig. The experimental work for DDVP was actually carried out in a series of several independent laboratory tests between 1988 and 1992. None of these tests complied with Good Laboratory Practice (GLP) and the data were not Quality Checked (QC'd). Following a recent visit to the University of Oslo to meet with all the study authors, some additional details of this experimental work with DDVP, which were not documented in the published paper, are clarified below:

- Pregnant female guinea pigs at about day 30 of gestation were delivered to the testing laboratory, on an as needed basis, from an animal supplier in Sweden. This period of gestation was chosen as it was believed to be the most stable for transportation and pregnancy at this point could be confirmed by palpation. There was no knowledge or documentation of the sire(s) that was used for the matings and the actual dates of matings were unconfirmed. All the pregnant females had littered previously and were apparently mated on the day of delivery of their previous litter.

- From all of the experiments, DDVP was administered to a total of four pregnant guinea pigs on specified days of gestation at the following dose levels:-

Number Of Guinea Pigs	DDVP (mg/kg) Dosed on Day 42	DDVP (mg/kg) Dosed on Day 43	DDVP (mg/kg) Dosed on Day 44	DDVP (mg/kg) Dosed on Day 45	DDVP (mg/kg) Dosed on Day 46	COMMENT: In-life Clinical observations And Actions
1	15	15	15	N/T	N/T	Clinical signs: Salivation and involuntary jaw movements
1	20	N/T	N/T	N/T	N/T	Terminated: Severe tremors
1	30 (15 + 15)	30 (15 +15)	30 (15+15)	N/T	N/T	Clinical signs: Severe salivation, and involuntary jaw movements
1	N/T	N/T	30 (15+15)	30 (15+15)	20 (15+5)	Clinical signs: Severe salivation, involuntary jaw movements and tremors

N/T not tested
( ) Dose was administered as a split dose at 12-hour intervals in each specified day

- DDVP (99%) analytical grade material was used for the test dosing solutions. These dosing solutions were made up daily but were not analysed for the actual DDVP concentrations. The dosing vehicle used was 20% ethanol in saline for both the DDVP and the control administered doses.

- The route of compound administration to the pregnant guinea pigs was subcutaneous for all the DDVP administered doses and also for the control doses in these experiments. None of the DDVP treated guinea pigs were protected at any time during the course of these experiments with any accompanying atropine administration, to inhibit the cholinergic signs. This procedure was however carried out for other organophosphates that were tested.

- The rationale for the DDVP dose selection used in their experiments was taken directly from an article in the published literature *Sterri S.H.,1981. Factors Modifying the Toxicity of Organophosphorus Compounds Including Dichlorvos. Acta. pharmacol. et toxicol. 49, suppl. V, 67-71.* No preliminary dose range finding or investigatory studies were performed in this laboratory to establish the toxicity of DDVP when administered to the pregnant guinea pig.

- Only data from three pregnant guinea pigs was used to support the results presented in the published paper.

- The authors concluded unanimously that the dose level of 15-mg DDVP/kg/day administered to the pregnant guinea pig on days 42 to 44 of gestation showed no effects on brain weight in the newly born guinea pigs. They confirmed this was a NOEL (no observed effect level) for prenatal brain development.

- The dose level of 20-mg DDVP/kg/day administered to the pregnant guinea pig on day 42 of gestation was found to be too toxic to continue the experiment. This guinea pig showed severe clinical signs of whole body tremors after dosing which necessitated the termination and abandonment of this dose level. No further testing was carried at this dose level and thus no evaluations on prenatal brain development in the pregnant guinea pig could be made.

- The author's then decided on a modified dosing regimen in order to overcome the inherent acute toxicity of DDVP in the pregnant guinea pig. They decided on a spit-dosing regimen administering DDVP at 12 hourly intervals during the specified day of gestation. As a result, a higher dose level of 30-mg DDVP/kg/day was then administered to two pregnant guinea pigs. One guinea pig managed to sustain a split dose of 15-mg DDVP/kg every 12 hours, for days 42 to 44 of gestation. For the other guinea pig however this dose level had to be reduced to 20-mgDDVP/kg/day with the split-dosing regimen of 15 reduced to 5-mg DDVP/kg for the last dose, due to severe clinical signs.

- Individual dam and pup data for the DDVP treated guinea pigs were not available for examination although this was requested prior to the laboratory visit. In fact throughout the entire visit no written study data books or records were available for inspection.